CERTIFICATE

This is to certify that the dissertation entitled

FORMULATION AND EVALUATION OF FAST DISINTEGRATING TABLETS OF NAPROXEN SODIUM

Constitutes the original work carried out by

(Reg. No-26106805)

Under the guidance and supervision of

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LIST OF ABBREVIATIONS

Cm	Centimetre
^{o}C	Degree Celsius
CCS	Croscaramellose sodium
CP	Crospovidone
DT	Disintegration time
Fig.	Figure
FTIR	Fourier transform Infra Red
gm	Gram
hrs	Hours
HCL	Hydrochloric acid
L	Liter
M	Molar
Meq	Milli equivalent
mg	Milligram
min	Minutes
ml	Milliliter
Mw	Molecular weight
N	Normality
nm	Nanometer
pH	Negitive logarithm of hydrogen ion concentration
FDT	fastly Disintegrating Tablet
RH	Relative humidity
rpm	Rotations per minute

1. INTRODUCTION

Fast-disintegrating and fast-dissolving tablets are becoming popular as novel delivery systems for drug administration. They are more convenient for children, elderly patients, patients with swallowing difficulties, and in the absence of potable liquids. The most desirable formulation for use by the elderly is one that is easy to swallow easy to handle. Taking these requirements into consideration, attempts have been made to develop a fast-disintegrating tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place. For example, it can be taken anywhere at anytime by anyone who do not have easy access to water. It is also easy to dose the aged, bed-ridden patients, or infants who have problems swallowing tablets and capsules. Recently, many companies have researched and developed various types of fast-disintegrating dosage forms.[1]

These tablets display a fast and spontaneous de-aggregation in the mouth, soon after the contact with saliva, though they can be handled or extracted from the package without alteration. The active agent can thus rapidly dissolve in the saliva and be absorbed through whatever membrane it encounters, during deglutition, unless it is protected from pre-gastric absorption. To fulfill these requirements, tablets must be highly porous, incorporating hydrophilic excipients, able to rapidly absorb water for a rapid deaggregation of the matrix. Different technological techniques, such as freeze drying or moulding or direct compression are currently employed to prepare the formulations of this type present on the pharmaceutical market.

Honda and Nakano reported that a half of the patients surveyed experienced difficulty in taking medication and felt that a tablet was a better and easier formulation compared to other formulations such as capsules or powders. Sugihara reported that the degree of ease when taking a tablet depended on its size. He reported that the size of tablet that was easiest to swallow was 7–8 mm, but the size easiest to handle was one larger than 8 mm.

1.1. Advantages of Fast Disintegrating Drug Delivery System (FDDS) [1-3]

1. Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients, mentally ill, disabled and uncooperative.
2. Convenience of administration and accurate dosing as compared to liquids.
3. No need of water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water.

4. Good mouth feel property of FDDS helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.
5. Ability to provide advantages of liquid medication in the form of solid preparation.
6. Rapid dissolution of drug and absorption, which may produce rapid onset of action.
7. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increased.
8. Ability to provide advantages of liquid medication in the form of solid preparation.
9. Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

1.2. Characteristics of fast disintegrating systems [2-5]

a. Ease of administration

Fast disintegrating drug delivery Systems are easy to administer and handle hence, leads to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (Tablets, capsules, solutions and suspensions) because of tremors of extremities and dysphasia. Fast Dissolving Delivery Systems may offer a solution for these problems.

b. Taste of the medicament

As most drugs are unpalatable, fast disintegrating drug delivery systems usually contain the medicament in taste masked form. These delivery systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of the drugs becomes critical to patient compliance.

c. Hygroscopicity

Several fast dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal condition from humidity which calls for specialized product packaging.

d. Friability

In order to allow fast disintegrating tablets to dissolve in the mouth, they are made of either very porous and soft- moulded matrices or compressed into tablets with very low

compression force, which makes the tablets friable and/or brittle which are difficult to handle, often requiring specialized peel-off blister packaging.

e. Mouth feel

Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth feel by reducing the "dryness" of a product.

Table No: 1 Various therapeutic areas in which the fast disintegrating dosage forms are available

Target population	Therapeutic areas
Pediatric	Antibiotics Anti-asthmatics Cough/Cold/Allergy Anti-epileptics Analgesics/Antipyretics Antidepressants
Adult & Elderly	Parkinson's Antimigraine Alzheimer's Anti-emetics Cancer Diabetes AIDS Gastric Relief Psychotherapeutics Cardiovascular Cough/Cold/Allergy Analgesics/NSAIDS

1.3. Approaches for fast disintegrating tablets [2-6]

A. Patented technologies

Currently, four fast-dissolving/disintegrating technologies have reached the U.S. market:

1) Zydis (R.P. Scherer, Inc.)

2) WOWTAB (Yamanouchi Pharma Technologies, Inc.)

3) OraSolv (Cima Labs, Inc.)

4) DuraSolv (Cima Labs, Inc.)

B. Three others are available outside the U.S.

1) Flash Dose (Fuisz Technologies, Ltd.),

2) Flash tab (Prographarm Group),

3) OraQuick (KV Pharmaceutical Co., Inc.)

4) Nanocrystal Technology

C. Conventional technologies

1.Freeze –drying or lyophilization

2. Tablet Molding

3. Direct compression

4. Spray drying

5. Sublimation

6. Mass extrusion

A. Patented technologies

1. Zydis technology

Zydis the best known of the fast-dissolving/disintegrating tablet preparations was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. The Zydis formulation is also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth. A major claim of the Zydis product is increased bioavailability

compared to traditional tablets. Because of its dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of pregastric absorption from this formulation. Buccal, pharyngeal and gastric regions are all areas of absorption of the Zydis formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism. However, if the amount of swallowed drug varies, there is the potential for inconsistent bioavailability. While the claimed increase in bioavailability is debatable, it is clear that the major advantage of the Zydis formulation is convenience. The amount of drug that could be incorporated should generally be less than 60 mg for soluble drugs. The partical size of the insoluble drugs should be less than 50mm and not more than 200mm to prevent sedimentation during processing. There are some disadvantages to the Zydis technology. The process of freeze-drying is a relatively expensive manufacturing process. As mentioned earlier, the Zydis formulation is very lightweight and fragile, and therefore should not be stored in backpacks or the bottom of purses. Finally, the Zydis formulation has poor stability at higher temperatures and humidities. It readily absorbs water, and is very sensitive to degradation at humidities greater than 65%.

2. Wowtab technology

The Wowtab fast-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. Wowtab technology is patented by Yamanouchi Pharmaceutical Co. The WOW in Wowtab signifies the tablet is to be given “With out Water”. It has just recently been introduced into the U.S. The Wowtab technology utilizes sugar and sugar-like (e.g; mannitol) excipients. This process uses a combination of low mouldability saccharides (rapid dissolution) and high mouldability saccharide (good binding property).The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate. Due to its significant hardness, the Wowtab formulation is a bit more stable to the environment than the Zydis or OraSolv. It is suitable for both conventional bottle and blister packaging. The taste masking technology utilized in the Wowtab is proprietary, but claims to offer superior mouth feel due to the patented smooth melt action. The Wowtab product dissolves quickly in 15 seconds or less.

2. OraSolv technology

OraSolv was Cima's first fast-dissolving/disintegrating dosage form. The OraSolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible

effervescence. The OraSolv technology is best described as a fast-disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The taste masking associated with the OraSolv formulation is two-fold. The unpleasant flavor of a drug is not merely counteracted by sweeteners or flavors; both coating the drug powder and effervescence are means of taste masking in OraSolv. This technology is frequently used to develop over-the-counter formulations. The major disadvantage of the OraSolv formulations is its mechanical strength. The OraSolv tablet has the appearance of a traditional compressed tablet. However, the OraSolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. For that reason, Cima developed a special handling and packaging system for OraSolv. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing. Lyophilization and high degrees of compression, as utilized in OraSolv's primary competitors, may disrupt such a taste masking approach. The OraSolv technology is utilized in six marketed products. These formulations can accommodate single or multiple active ingredients and tablets containing more that 1.0 g of drug have been developed. Their disintegration time is less than 30s.The OraSolv formulations are not very hygroscopic.

3. DuraSolv technology

DuraSolv is Cima's second-generation fast-dissolving/disintegrating tablet formulation. Produced in a fashion similar to OraSolv, DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. DuraSolv tablets are prepared by using conventional tabletting equipment and have good rigidity (friability less than that 2%). The DuraSolv product is thus produced in a faster and more cost-effective manner. DuraSolv is so durable that it can be packaged in traditional blister packaging, pouches or vials.

One disadvantage of DuraSolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction. Unlike OraSolv, the structural integrity of any taste masking may be compromised with high drug doses. The drug powder coating in DuraSolv may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds. Therefore, the DuraSolv technology is best suited for formulations including relatively small doses of active compound.

B. Three others are available outside the U.S.

1. Flash dose technology

Fuisz Technologies has three oral drug delivery systems that are related to fast dissolution. The first two generations of quick-dissolving tablets, Soft Chew and EZ Chew, require some chewing. However, these paved the way for Fuisz's most recent development, Flash dose. The Flash dose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This procedure has been patented by Fuisz and is known as Shearform. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue.

Flash dose tablets consist of self–binding shear form matrix termed as "floss". Shear form matrices are prepared by flash heat processing and are of two types. Single floss or Unifloss, consisting of a carrier, and two or more sugar alcohols, of which one is xylitol. Dual floss consists of a first shear form carrier material (termed "base floss", contains a carrier and at least one sugar alcohol generally sorbitol), and a second shear form binder matrix ("binder floss", contains a carrier and xylitol).

Interestingly, by changing the temperature and other conditions during production, the characteristics of the product can be altered greatly. Instead of a floss-like material, small spheres of saccharides can be produced to carry the drug. The process of making microspheres has been patented by Fuisz, and is known as CEFORM and serves as an alternative method of taste masking.

2. Flash tab technology

Prographarm laboratories have patented the Flashtab technology. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and micro encapsulation. The microcrystals of microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets. All the processing utilized the conventional tabletting technology, and the tablets produced are reported to have good mechanical strength and disintegration time less than one minute.

3. OraQuick

The OraQuick fast-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceutical claims its microsphere technology, known as MicroMask, has superior mouth feel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/disintegrating technologies makes OraQuick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. OraQuick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, Psycho tropics, and Anti-infectives.

4. Nano Crystal technology

For fast dissolving tablets, Elan's proprietary Nano Crystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using Nano Crystal technology. Nano Crystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling the drug substance using a proprietary wet milling technique.

Nano Crystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded As Safe) ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds. This approach is especially attractive when working with highly potent or hazardous materials because it avoids manufacturing operations (e.g; granulation, blending, and tableting) that generate large quantities of aerosolized powder and present much higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into ODT dosage forms because manufacturing losses are negligible.

C. Conventional technologies

1. Freeze drying

A process, in which water is sublimated from the product after freezing, is called freeze drying. Freeze-dried forms offer more rapid dissolution than other available solid products. The lyophilization process imparts glossy amorphous structure to the bulking agent and some times to the drug, thereby enhancing the dissolution characteristics of the formulation. However, the use of freeze drying is limited due to high cost of the equipment and processing. Other major disadvantages of the final dosage forms include lack of physical resistance in standard blister packs.

A tablet that rapidly disintegrates in aqueous solution includes a partially collapsed matrix network that has been vacuum dried above the collapse temperature of the matrix. The matrix is partially dried below the equilibrium freezing point of the matrix. Vacuum drying the tablet above its collapse temperature instead of freeze drying below its collapse temperature provides a process for producing tablets with enhanced structural integrity, while rapidly disintegrating in normal amounts of saliva.

2. Moulding

Tablets produced by moulding are solid dispersions. Physical form of the drug in the tablets depends whether and to what extent, it dissolves in the molten carrier. The drug can exist as discrete particles or micro particles dispersed in the matrix. It can dissolve totally in the molten carrier to form solid solution or dissolve partially in the molten carrier and the remaining particles stay undissolved and dispersed in the matrix. Disintegration time, drug dissolution rate and mouth feel will depend on the type of dispersion or dissolution.

Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is, in general, made from water soluble sugars. Moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs.

Moulded tablets usually are prepared from soluble ingredients by compressing a powder mixture previously moistened with solvent (usually water or ethanol) into mould plates to form wetted mass (compression moulding). Recently moulded forms also have been prepared directly from the molten matrix in which the drug is dissolved or dispersed (heat moulding) or by evaporating the solvent from the suspension at standard pressure (no-vacuum lyophilization).

3. Direct compression[4-7]

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressed tablet's disintegration and solubilization depends on single or combined action of disintegrates, water soluble excipients and effervescent agent. Disintegrate efficacy is strongly affected by tablet size and hardness. Large and hard tablets have disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and /or high friability and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister alveolus, all result from insufficient physical resistance.

Disintegrants have major role in the disintegration and dissolution process of mouth dissolving Tablets made by direct compression. To ensure a high disintegration rate, choice of suitable type and an optimal amount of disintegrant is important. Other formulation components such as water soluble excipients or effervescent agents can further enhance dissolution or disintegration properties. But main drawback of using effervescent excipients is their highly hygroscopic nature.

The understanding of disintegrant properties and their effect on formulation has advanced during last few years, particularly regarding so called superdisintegrants. Disintegration efficiency is based on force equivalent concept, which is the combined measurement of swelling force development and amount of water absorption. Force equivalent expresses the capability of disintegrant to transform absorbed water into swelling force. The optimization of tablet disintegration was defined by means of disintegrant critical concentration. Below this concentration, the tablet disintegration time is inversely proportional to disintegrate concentration and above that disintegration time remains approximately constant or even increases.

The simultaneous presence of disintegrate with a high swelling force called disintegrating agent and substances with low swelling force (starch, cellulose and direct compression sugar) defined as, "swelling agent" was claimed to be a key factor for rapid disintegration of tablet, which also offers physical resistance.

4. Spray-drying

Highly porous and fine powders can be produced by spray drying, as the processing solvent is evaporated rapidly during spray drying. Spray drying technique has been employed to prepare fast dissolving tablets. They developed formulation by using mannitol as bulking agent, hydrolysed and non-hydrolysed gelatin as support matrix, sodium starch glycolate as disintegrant and acidic material (eg; citric acid) and/or alkali material (eg; $NaHCO_3$) to enhance disintegration and dissolution. When immersed in an aqueous medium, the tablets compressed from spray-dried powder, disintegrated within 20 seconds.

5. Sublimation

Because of low porosity, compressed tablets composed of highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in the water. Porous tablets that exhibit good mechanical strength and dissolve quickly have been developed. Inert solid ingredients (e.g.; urea, urethane, ammonium carbonate, camphor, naphthalene) were added to other tablet excipients and the blend was compressed into tablet. Removal of volatile material by sublimation generated a porous structure.

A method of producing fast dissolving tablet using water as the pore forming material has been described by Makino. Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. The tablets dissolve within 10-20 seconds and exhibit sufficient mechanical strength for practical use. Koizumi have developed a new method of preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material.

6. Mass-extrusion

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

1.4. Taste masking technologies in Oral Pharmaceuticals

Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that are encountered with

certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients.

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist.

A. General taste masking practices in Oral Pharmaceuticals

Various techniques available for masking bitter taste of drugs include taste masking with ingredients such as flavors, sweeteners, and amino acids; taste masking by polymer coating; taste masking by conventional granulation; taste masking with ion-exchange resins; taste masking by spray congealing with lipids; taste masking by formation of inclusion complexes with cyclodextrins; taste masking by the freeze-drying process; taste masking by making multiple emulsions; and taste masking with gelatin, gelatinized starch, liposomes, lecithins or lecithin-like substances, surfactants, salts, or polymeric membranes.

1. Taste masking with flavors, sweeteners, and amino acids

This technique is the foremost and the simplest approach for taste masking, especially in the case of pediatric formulations, chewable tablets, and liquid formulations. But this approach is not very successful for highly bitter and highly water soluble drugs. Artificial sweeteners and flavors are generally being used along with other taste-masking techniques to improve the efficiency of these techniques. The cooling effect of the taste masking agents also aids in reducing the bitterness. Menthol reduces the bitter taste, and low-calorie formulations show beneficial effects.

Aspartame is used as a prominent sweetener in providing bitterness reduction. A very small concentration (0.8%) is effective in reducing the bitterness of 25% acetaminophen. Starch, lactose, and mannitol have also exhibited taste-masking properties of caffeine.

Artificial sweeteners such as neohesperidine dihydrochalcone and hesperidine dihydrochalcone 4'-β-D glucoside have the ability to mask bitterness and saltiness by virtue of their lingering sweetness.

2. Taste masking with lipophilic vehicles

Oils, surfactants, polyalcohols, and lipids effectively increase the viscosity in the mouth and coat the taste buds, and therefore they are potential taste masking agents.

1. Guaifenesin Melt granulation Carnauba wax and magnesium aluminium silicate.
2. Cimetidine Granulation Glyceryl monostearate.

Lecithin and Lecithin-like Substances Formulations with a large excess of lecithin or lecithin-like substances are claimed to control bitter taste in pharmaceuticals. Magnesium aluminum silicate with soybean lecithin is used to mask the unpleasant taste of Ampicillin HCl. The drug is dissolved in or dispersed into an organic solvent such as chloroform.

3. Taste masking by coating with hydrophilic vehicles

This is the simplest and most feasible option to achieve taste masking. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. Coating of chewable tablets provides excellent taste masking while still providing acceptable bioavailability. A specialized technique, i.e., micro emulsion technology, has been used for taste masking of powders, chewable tablets, and liquid suspensions.

4. Carbohydrates (Cellulose)

The taste of orally administered drugs can be masked by coating the drug with carbohydrates. Bitter solid drugs such as pinaverium bromide, a spasmolytic, has no bitter taste when formulated in an organoleptically acceptable manner by polymer coating with a mixture of cellulose or shellac and a second film forming polymer soluble at pH less than 5.

Taste masking of ibuprofen has been successfully achieved by using the air-suspension coating technique to form microcapsules, which comprise a pharmaceutical core of crystalline ibuprofen and a methacrylic acid copolymer (Eudragit) coating that provides chewable taste-masked characteristics.

5. Taste masking by inclusion complexation

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent, i.e., the host molecule, forming a stable complex. The complexing agent is capable of masking the bitter taste of drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds, thereby reducing the perception of bitter taste. This method is most suitable only for low dose drugs. Vander waals forces are mainly involved in inclusion complexes. β-cyclodextrin is the most widely used complexing agent for inclusion type complexes. It is a sweet, nontoxic, cyclic oligosaccharide obtained from starch.

The strong bitter taste of carbetapentane citrate syrup was reduced to approximately 50% by preparing a 1:1 complex with cyclodextrin. Palatable ibuprofen solutions are

prepared by forming a 1:11 to 1:15 inclusion complex with ibuprofen and hydroxypropyl β-cyclodextrin, respectively. The complex masked the bitter component but created a sore taste that was masked by sweeteners.

6. Taste masking by Ion-exchange resins (IERs)[6,8]

Ion-exchange resins (IERs) are high molecular weight polymers with cationic and anionic functional groups. The most frequently employed polymeric network is a copolymer of styrene and divinylbezene. Ion-exchange resins are used in drug formulations to stabilize the sensitive components, sustain release of the drug, disintegrate tablets, and mask taste. Drug can be bound to the resin by either repeated exposure of the resin to the drug in a chromate graphic column or by prolonged contact of resin with the drug solution.

Drugs are attached to the oppositely charged resin substrate, forming insoluble adsorbates or resonate through weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary pH conditions. This suitably masks the unpleasant taste and odor of drugs.

Drug release from the resin depends on the properties of the resin and the ionic environment within the gastrointestinal tract (GIT). Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GIT, followed by diffusion of free drug molecule out of the resins.

Ion exchange resins can be classified into four major groups:

- Strong acid cation-exchange resin.
- Weak acid cation-exchange resin.
- Strong base anion-exchange resin.
- Weak base anion-exchange resin.

B. Miscellaneous taste-masking approaches

1. By effervescent agent

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have also been employed for use as taste-masking agents for dosage forms that are not dissolved in water prior to administration. A chewing gum composition of bitter medicament(s) was formulated to supply the medicament(s) to the oral cavity for local application or for buccal absorption. It comprises a chewing gum base, an orally administrable medicament, a taste masking generator of carbon dioxide, and

optionally a taste bud desensitizing composition (e.g; oral anesthetics such as benzocaine and spilanthol) and other non active materials, such as sweeteners, flavoring components, and fillers. Recently, effervescent tablets of fentanyl and prochlorperazine were developed to supply these drugs to the oral cavity for buccal, sublingual, and gingival absorption. The formulations contain the drugs in combination with effervescent agent(s) to promote their absorption in the oral cavity and to mask their bitter taste.

2. Salt preparation

Salt preparation is one of the classical approaches to mask the bitter taste of drug by either decreasing solubility or by increasing hydrophobicity and thereby reducing contact of bitter drugs with taste buds. This approach differs others to modify the chemical composition of the drug substance itself, so as to render it less soluble in saliva and thereby less stimulating to the taste buds, or to obtain a tasteless or less bitter form. Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water-soluble ibuprofen salts in aqueous solution. The bitter taste of caffeine may be masked by formulating it as a carbonated oral solid preparation using sodium bicarbonate, ascorbic acid, citric acid, and tartaric acid. Magnesium aspirin tablets are rendered tasteless by preparing magnesium salts of aspirin.

3. Solid dispersion systems

Solid dispersions can be defined as the dispersion of one or more active ingredients in an inert solid carrier. Solid dispersion of drug with the help of polymers, sugar, or other suitable agents, is very useful for taste masking. The bitter taste of dimenhydrinate can be masked by preparing the solid dispersion of the drug with polyvinyl acetate phthalate.

4. Group alteration and prodrug approach

The alkyloxyalkyl carbonates of the Clarithromycin 2’ position have remarkably alleviated bitterness and improved bioavailability when administered orally.

Tasteless/ bitter less prodrugs of opioid analgesics and antagonists were formulated for improved buccal delivery. Tasteless prodrugs of Nalbuphine HCl, Naltrexone, Naloxone, Oxymorphone HCl, Butorphanonol, and Levallorphan were synthesized for buccal administration to improve bioavailability relative to that of oral dosing without the characteristic bitter taste. In rats, the prodrugs demonstrated up to 90% bioavailability. It was

concluded that when administered as prodrugs, bioavailability improved without visible adverse effects.

5. Freeze drying process

This method is used to develop fast-dissolving oral technologies such as Zydis and Lyoc technology. Zydis is a tablet-shaped dosage form that spontaneously disintegrates in the mouth in seconds. This is due to the high porosity produced by the freeze drying process.

The Zydis process requires the active ingredient to be dissolved or suspended in an aqueous solution of water-soluble structure formers. The resultant mixture is then poured into the preformed blister pockets of a laminate film and freeze dried. The two most commonly used structural excipients are gelatin and mannitol, although other suitable excipients can be used (e.g; starches, gums, etc.). This process is ideally suited to low solubility drugs as these are more readily freeze dried.

6. Wet spherical agglomeration (WSA) technique and continuous multipurpose melt (CMT) technology

A novel micro encapsulation process combined with the wet spherical agglomeration (WSA) technique was used to mask the bitter taste of Enoxacin.

1.5. Mechanism of tablet disintegration and water absorption

When mouth dissolving tablets placed in the mouth, upon contact with saliva the tablets disintegrates or dissolve instantaneously. There are four mechanisms involved in the tablet disintegration mechanisms

a) Swelling
b) Wicking (capillary)
c) Deformation
d) Chemical reaction (acid base reaction)

a. Swelling

Not all disintegrates swell in contact with water swelling is believed to be a mechanism in which; certain disintegrating agents (like starch) impart their disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to disintegrate.

b. Wicking (porosity and capillary action)

Effective disintegratnts that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablets porosity provides way for the penetration of fluid into tablets. The disintegrants particles (with cohesiveness and compressibility) themselves act to enhance porosity and provide these capillaries into the tablets. Liquid is drawn up or wicked into these ways by capillary action and rupture the inter-particulate bonds causing the tablet to break into small parts.

c. Deformation

Starch grains are generally thought to be "elastic" in nature that is the grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression forces involved in tabletting, these grains are permanently deformed and are said to be "energy rich" with these energy being released upon exposure to water, that is the ability for starch to swell is higher in "energy rich" starch grains than in starch grains that have not been deformed under pressure. It is belived that no single mechanism is responsible for the action of most disintegrants. But rather, it is more likely the results of inter-relationships between these major mechanisms.

E. Chemical reaction (acid base reaction)

Disintegration of tablet is inclusion of citric acid and tartaric acid along with the sodium bicarbonate, sodium carbonate, potassium carbonate; these react in contact with water to liberate carbon dioxide that disrupts the tablet.

F. Factors affecting action of disintegrants

- ✓ Percentage of disintegrants presents in the tablets
- ✓ Type of substances present in the tablet
- ✓ Combination of disintegrants
- ✓ Presence of surfactants
- ✓ Hardness of the tablet
- ✓ Nature of drug substances.

Table No:2 Marketed fast disintegrating tablets[9]

Name of the Product	Active Ingredients
Imodium Lingual	Imodium
Pepcidin Rapitab	Quick releasing antiulcer preparation of pepcid
Mosid – MT	Mouth melt tablet of Mosapride citrate.
Calritin Reditabs	Immediate Dissolving formulation of Calritin
Nimulid – MD	Nimesulide
Zyrof Meltab	Rofecoxib
Claritin Reditab	Micronized loratadine
Feldene Melt	Piroxicam (10 or 20 mg),
Maxalt-MLT	Rizatriptan (5 or 10 mg), peppermint flavor
Pepcid RPD	Famotidine (20 or 40 mg),
Zyprexa Zydis	Olanzapine (5, 10, 15 or 20 mg),
Zofran ODT	Ondansetron (4 or 8 mg), strawberry flavor
Remeron Soltab	Mirtazepine (15, 30, or 45 mg), orange flavor
Tempra FirstTabs	Acetaminophen (80 or 160 mg), (currently available in Canada)
NuLev	Hyoscyamine sulfate (0.125 mg), mint flavoring
Zomig ZMT	Zolmitriptan (2.5 mg), orange flavor

2. LITERATURE REVIEW

Yoshio et.al., (2008) evaluated the effect of lubricants on the characteristics of orally disintegrating (OD) tablets manufactured using the phase transition of sugar alcohol. OD tablets were produced by directly compressing a mixture containing lactose–xylitol granules, disintegrant, glidant and lubricant, and subsequent heating. The effect of the type of lubricant on the tablet characteristics was evaluated using magnesium stearate (mg-st), sodium stearyl fumarate (SSF), and talc as lubricants. the hardness of the tablets increased to ca. 6 kp as a result of heating, regardless of the kind of lubricant. the oral disintegration time of the tablets containing mg-st or ssf increased with an increase in the hardness. In contrast, the oral disintegration time of the tablets containing talc was not changed despite of an increase in hardness. The water absorption rate of the tablets containing talc was much faster than that of the tablets containing other lubricants. The water absorption rate of the tablets containing talc was also increased by heating.[12]

Yoshio et.al., (2008) evaluated the effect of preparation method on the properties of orally disintegrating (OD) tablets, OD tablets were prepared by compressing a mixture of high melting point sugar alcohol (HMP-SA) and low melting point sugar alcohol (LMP-SA) and subsequent heating. In the direct compression method (DCM) where the LMP-SA was added as a powder, both hardness and disintegration time were increased by decreasing the particle size of the LMP-SA. In the wet granule compression method (WGCM), where the LMP-SA was added as an aqueous binder solution, the tablets became harder with less heating compared to tablets prepared by DCM. Using 1% xylitol as the LMP-SA provided tablets with sufficient hardness when prepared by WGCM, as opposed to DCM where 5% xylitol was necessary to prepare tablets with similar hardness. These results suggest that uniformly distributed LMP-SA on the surface of HMP-SA particles in WGCM might diffuse more easily during the heating process compared to mechanically mixed LMP-SA in DCM, resulting in an increase in tablet hardness even with a short heating time and low content of LMP-SA. In addition, disintegration and hardness stability of the tablets were affected by the LMP-SA content when prepared by WGCM, suggesting that the LMP-SA content should be regulated to assure the stability of OD tablet characteristics[13].

Jianchen et.al., (2008) evaluated the potential of microspheres for taste masking when incorporated into orally disintegrating tablets. The microspheres were produced by spray drying a mixture of the model compound (famotidine) with taste masking material. The spray process was optimized using a central composite design for two variables to obtain microspheres with desirable characteristics. Then the microspheres were mixed with other excipients to form orally disintegrating tablets. The optimal spray-drying process parameters were 34 mg/ml for solid concentration and 7 ml/min for feed rate. The drug encapsulation efficiency of the spray-dried microspheres ranges from of 37.59 to 61.56%, with a mean diameter of less than 10m size and low moisture content (less than 4%). Results from an evaluation by a panel of six human volunteers demonstrated that the orally disintegrating tablets with taste masking microspheres improved the taste significantly. Furthermore, an in vivo study in rats showed that the microspheres neither decrease the bioavailability nor retard the release of famotidine significantly. In conclusion, spray-dried microspheres can effectively mask the bitter taste of the active pharmaceutical ingredients in combination with the orally disintegrating tablets[14].

Riikka et.al., (2008) have studied, the dissolution rate of a poorly soluble drug, perphenazine (PPZ) was improved by a solid dispersion technique to permit its usage in intraoral formulations. Dissolution of PPZ (4 mg) in a small liquid volume (3 ml, pH 6.8) within one minute was set as the objective. PVP K30 and PEG 8000 were selected for carriers according to the solubility parameter approach and their 5/1, 1/5 and 1/20 mixtures with PPZ (PPZ/polymer w/w) were prepared by freeze-drying from 0.1 N HCl solutions. The dissolution rate of PPZ was improved with all drug/polymer mixture ratios compared to crystalline or micronized PPZ. A major dissolution rate improvement was seen with 1/5 PPZ/PEG formulation, i.e. PPZ was dissolved completely within one minute. SAXS, DSC and XRPD measurements indicated that solid solutions of amorphous PPZ in amorphous PVP or in partly amorphous PEG were formed. DSC and FTIR studies suggested that PPZ dihydrochloride salt was formed and hydrogen bonding was occurred between PPZ and the polymers. It was concluded that molecular mixing together with salt formation promoted the dissolution of PPZ, especially in the case of the 1/5 PPZ/PEG dispersion, making it a promising candidate for use in intraoral formulations[15].

Adam et.al., (2007) formulated the fast dispersible/slow releasing ibuprofen tablets. To prevent bitter taste and side effects of the drug, the drug was associated with Phospholipon 80H, a

saturated lecithin, by wet granulation. The granules were then coated using different film forming agents (Kollicoat SR 30, Amprac 01, Kollidon 90F, Eudragit RD 100) obtaining four lots 1–4. Coated granules were then formulated with a sweetener (Aspartame), a mannitol-based diluent (Pearlitol SD 200) and Kollidon CL (1-4K) or Explotab (1-4E) were added as superdisintegrants and compacted under low compression force. By an appropriate combination of excipients it was thus possible to obtain orally disintegrating tablets and a delayed release of ibuprofen using simple and conventional techniques[16].

Seong et.al., (2007) have developed a complex formation between drugs and ion-exchange resins was investigated and the effects of coating by various aqueous polymeric dispersionson the complexes were evaluated for developing new sustained-release fast-disintegrating tablets (FDTs). Complexes of ion-exchange resin and dextromethorphan, a model drug, were prepared using different particle sizes of the resins. As the particle size of resins increased, the drug loading and release rate decreased due to the reduced effective diffusion coefficient and surface area. When the drug release profiles were applied into Boyd model and Higuchi equation, the linear relationship was observed, indicating that the diffusion within the resin matrix is the rate-controlling step[17].

Devi et.al., (2006) were prepared oro dispersable flucanozole tablets. Oro dispersable tablets of flucanozole were prepared with two different volatilizable compound viz, ammonium chloride,and camphor. Eight formulations were prepared with varying concentration of volatalizable substances by wet granulation. These tablets were evaluated for their friability, weight variation, hardness, disintegration time, and pH of the solution after dispersion, the best formulation were choosen and compared with marketed conventional tablets.These oro dispersable fluconazole tablets can be focused for treating of oral fungal infections particularly in premature infants, geriatrics bed ridden patients, patients receiving immuno suppressive therapy and AIDS patients[18].

Jinichi et.al., (2006) have developed a rapidly disintegration tablet in the oral cavity was prepared using a glycine as a disintegrant. Effect of disintegrant on the disintegration behavior of the tablet in the oral cavity was evaluated. It was suggested that the tablet formulation

containing carboxymethylcellulose (NS-300) and glycine was highly applicable to water-insoluble drug, such as ethenzamide[19].

Chaudari et.al., (2006) were prepared rizatriptan benzoate oral disintegrating tablets.Taste masked by using indion214 resin.They conducted the drug release studies at mouth salivary pH and at gastric pH. They obtain complete drug release at gastric pH[20].

Shishu et.al., (2006) were prepared compressed tablets of diazepam which disintegrate in the oral cavity were prepared using microcrystalline cellulose as directly compressible filler and sodium starch glycolate as super disintegrants. The taste is masked by preparing microspheres using amino alkyl methyl acrylate copolymer (Eudragit E-100) by solvent evoparation method. Taste evolutions of these microspheres were done by both spectrophotometric taste evolution technique and panel testing[21].

Prajapati et.al., (2006) were dispersible tablets of an insoluble drug nimesulide was prepared by wet granulation method. Using 0.5%w/v aqueous PVP K-30 as binder. Plkanatago ovata used as a superdisintegrating agent and compared with sodium starch glycolate, cross carmellose sodium Swelling index was investigated with an aim to evaluate super disintegrants from mucilage of plantago ovata and and compared with sodium starch glycolate, cross carmellose sodium. They showed highest swelling index indicating the required properties of disintegrants[22].

Masaaki et.al., (2005) were studied the factors affecting the characteristics of rapidly disintegrating tablets containing an amorphous ingredient prepared by crystalline transition method (CTM) under various storage conditions. Effect of storage conditions and formulating ratio of amorphous sucrose on the characteristic changes (tensile strength, porosity, and disintegration time) of the rapidly disintegrating tablets was studied. The storage conditions of different temperature and humidity affected the rate of crystalline transition and the increase in the tablet tensile strength. The faster crystalline transition resulted in a faster rate of increase in the tablet tensile strength. Regarding the effect of the formulating ratio of amorphous sucrose. In the case of 20–100%. Hence, the higher formulating ratio of amorphous sucrose provided the longer disintegration time in the mouth[23].

Takao et.al., (2005) have formulated a novel fast-disintegrating tablets. Saccharides can be divided into high- and low-compressibility categories, and an appropriate material for fast-disintegrating tablets was created by taking advantage of this fact. To improve the compressibility of low-compressibility saccharides, particle modification was conducted by coating and granulating a low-compressibility saccharide with a high one to enable the production of a fast-disintegrating tablet[24].

Mesut et.al., (2005) have prepared novel capsule-based fast disintegrating dosage forms for the oral cavity (Fastcaps). First, cast films were prepared from various additive-containing gelatin solutions and evaluated with respect to disintegration time and mechanical properties in order to identify suitable formulations for the capsule preparation. The disintegration time of films decreased with decreasing bloom strength and could be further decreased by the addition of sugars or PEGs. Fast disintegrating capsules were successfully prepared by a dipping process, whereby parameters such as the viscosity and temperature of the dipping solution and the dipping velocity of the steel pins were optimized. The required viscosity range of the dipping solution for Fastcap manufacturing was 500–600 cP. The addition of the hydrophilic additives (xylitol, sorbitol or PEG 1500) did not significantly affect the viscosity and gelation temperature of the dipping solution. The in vitro disintegration of Fastcaps (30–45 s) was twice as rapid as the one of regular hard gelatin capsules. In vivo, Fastcaps disintegrated rapidly (9–13 s). Lactose and/or microcrystalline cellulose were suitable fillers for Fastcaps. The mechanical properties of Fastcaps were similar to commercially available gelatin capsules, which assures good processability and handling[25].

Mishra et.al., (2005) were prepared rapidly disintegrating oral tablets of valdecoxib. Valdecoxib is a non-steroidal anti inflammatory property. Valdecoxib has poor aqueous solubility results in variable in dissolution rate. In this present work prepare fast disintegrating tablets using various super disintegrants following direct compreesion. All formulation showed disintegration time less than 60 sec. Along with rapid invitro dissolution. It was concluded that the fast disintegrateing tablets of the poorly soluble drugs can be made by direct compression technique using selective super disintegrants showing enhanced dissolution. And hence better compleance and effective therapy[26].

Chaudari et.al., (2005) were prepared fast dissolving tablets of famotidine. It is a H2 receptor antagonist. It inhibits acid production by reversibly competing with histamine for binding to H2 receptor on the baso lateral membrane of perietal cells. It is commonly used drug but the major disadvantage is its bitterness and low bioavalibilty. The bitter taste of famotidine was masked by preparing the solid dispersion using eudragit E-100. solid dispersion is prepared by solvent evaporation method. Taste evaluation is done by humanvolunteers using time intensity method[27].

Amin et.al., (2005) were prepared fast disintegrating dosage form of ofloxacin and metronidazole benzoate. Ofloxacin is a second generation floroquinolone, is a bitter anti bacterial. Taste is masked of ofloxacin by using cationic exchange resin(indion 204), In this work ion exchange resin Indian 414 used as super disintegrants. Comparative study with existing super disintegrants was carried out[28].

Dandagi et.al., (2005) were prepared rapidly disintegrating domperidone tablets. In this work rapidly disintegrating tablets were prepared by two methods 1) sodium starch glycolate and treated agar used as super disintegrants in mass extrusion technique.2) Treated agar methodall formulation show good palatable mouth feel, and rapid disintegrating time[29].

Vijaya et.al., (2005) were prepared disintegrating oral tablets of meloxicam. Meloxicam is an effective and selective cyclo oxygenase cox-2 inhibitor with anti inflammatory and analgesic properties. The poor aqueous solubility of the drug leads to variable dissolution rates. In this study an attempt has been made to prepare fast disintegrating tablets of meloxicam in the oral cavity with enhanced dissolution rate. The tablets were prepared with three super disintegrants, sodium starch glycolate, ac-di-sol, and low molecular weight hydroxy propyl methyl cellulose. The blend was examined for angle of repose, bulk density, tapped density, compressibility index, and hautionar ratio[30].

Kaushik et.al., (2004) were prepared olanzapine tablets which dissolves rapidly in mouth, there fore needing not be swallowed. Mouth dissolving tablets of olanzapine were prepared by effervescent formulation approach. The effervescent Excipient system not only rapid dissolution of tablets in the oral cavity also masks the slight bitter taste of medicament. Sodium bi carbonate, and citric acid were used as effervescent agents. Sodium bi carbonate and citric acid

in the formulation gave a soothing fizz, excellent mouth feel, good palatability, and quick dissolution profile[31].

Kucheka et.al., (2004) were developed mouth dissolving tablets of salbutamol sulphate, It is a selective b2 receptor agonist widely used as bronchodilator. Formulation was designed by factorial design technique.Sodium starch glycolate, crosscarmellose sodium, and treated ager werte used as super disintegrants. while micro crystalline cellulose was used as diluent. Direct compression technique was used as it requires conventional tablet machienary and thus economical process. Formulation containing sodium starch glycolate, along with other super disintegrants, showed rapid in vitro band invivo dispersion time, as compared to other formulation[32].

Mahajan et.al., (2004) were prepared mouth dissolve tablets of sumatriptan succinate. Prepared the tablets by using disintegrants sodium starch glycolate, carboxy methyl cellulose, and treated agar by direct compression method. The prepared tablets were evaluated for thickness, uniformity of weight, content uniformity, hardness, tensile strength, porosity, wetting time, water absorption ratio, in vitro and in vivo disintegrating time[33].

Beatrice et.al., (2002) have formulated the design carbamazepine fast-release tablets, prepared by melt granulation technique, involving the use of melt granulation process in high shear mixer for the production of tablets. In particular, the granules containing CBZ were prepared using polyethylene glycol (PEG) 4000 as a melting binder and lactose monohydrate as hydrophilic filler. The potential of the intragranular addition of crospovidone as a dissolution enhancer and a disintegrant agent was also evaluated. After the analysis of their solid state performed by means of X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC), However, the difficult disintegration and bad dissolution performance of the tablets not containing intragranular crospovidone highlight the necessity of this disintegrant in the granulating mixture. Moreover, the extragranular addition of a small amount of crospovidone gave rise to a further amelioration of the disintegration and dissolution performances[34].

3. AIM AND OBJECTIVE

Fast disintegrating tablets are becoming popular as one of the user friendly dosage forms. Our purpose is to develop an original composition of fast disintegrating tablet by using conventional tablet manufacturing process. The basic approach used in the development of fast disintegrating tablets is the use of superdisintegrants. Cros Carmellose Sodium, Sodium Starch Glycolate, and Crospovidone, low-subsititued Hydroxyl Propyl Cellulose were used in the present study. Before that, bitter taste of Naproxen sodium was masked by using sweetner.

This study was under taken with the aim to formulate and evaluate taste masked fast disintegrating tablets to avert the problems of swallowing and to provide rapid on set of action. The drug chosen for present study is Naproxen sodium.

The present work is to study the effect of various superdisintegrants on drug (Naproxen sodium) by direct compression methods. In the present study tablets will be prepared at approximately equal hardness.

The dissolution profiles of drug will be compared for tablets containing different superdisintegrants then to compare the effect of superdisintegrants on the in vitro dissolution and in vitro disintegration in pH 6.8 Phosphate buffer as dissolution medium.

4. PLAN OF WORK

- To prepare fast disintegrating tablets of Naproxen sodium using different super disintegrates.
- To select the method of taste masking.
- To select the formulation composition.
- To test all physical evaluation parameters.
- To construct the calibration curve for Naproxen sodium.
- To study the drug dissolution profile.
- To study the water absorption ratio.
- To study the determine disintegration time.
- To select the best formulation based on the above studies.

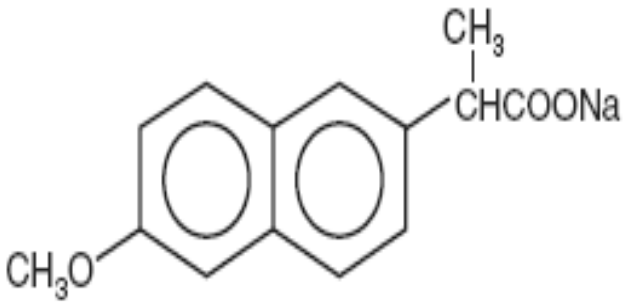
5. DRUG PROFILE

Non proprietary name: Naproxen sodium

Chemical name : (S)-6-Methoxy-alpha-methyl-2-naphthaleneacetic sodium salt

Molecular formula : $C_{14}H_{13}NaO_3$

Molecular weight : 252.24 g/mol



PHYSICOCHEMICAL PROFILE

Description : An odorless crystalline powder, white to creamy in color.

Melting point : 250-251 ºC

Solubility : It is soluble in methanol and water.

PHARMACODYNAMICS

The mechanism of action of Naproxen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity. Two unique cyclooxygenases have been described in mammals. The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity.

PHARMACOKINETICS

Although naproxen itself is well absorbed, the sodium salt form is more rapidly absorbed resulting in higher peak plasma levels for a given dose. After oral administration, plasma levels

of naproxen are detected within 30 minutes of dosing, with peak plasma levels occurring approximately 5 hours after dosing.

ABSORPTION

Naproxen itself is rapidly and completely absorbed from the GI tract with an *in vivo* bioavailability of 95%. Based on the pharmacokinetic profile.

DISTRIBUTION

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels, naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day, there is a less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses.

METABOLISM

Naproxen is extensively metabolized to 6-0-desmethyl Naproxen and both parent and metabolites do not induce metabolizing enzymes.

ELIMINATION

The elimination half-life of naproxen is approximately 15 hours. Steady state conditions are attained after 2-3 doses of Tablets. Most of the drug is excreted in the urine, primarily as unchanged naproxen (less than 1%), 6-0-desmethyl naproxen (less than 1%) and their glucuronide or other conjugates (66-92%). A small amount (< 5%) of the drug is excreted in the feces. The rate of excretion has been found to coincide closely with the rate of clearance from the plasma. In patients with renal failure, metabolites may accumulate.

USES: Naproxen sodium is used to relieve mild to moderate pain from various conditions (e.g; tendonitis, menstrual cramps). It also reduces pain, swelling, and joint stiffness caused by arthritis, bursitis, and gout. Reducing these symptoms helps you do more of your normal daily activities. This medication is known as a nonsteroidal anti-inflammatory drug (NSAID).

Table No:3 Dosage form and dose

Route	Dosage forms	Strength
Oral	Tablets,	220 mg
	Tablets	275 mg
	Tablets	550 mg
	Naproxen sodium controlled-release	550 mg/day

DRUG INTERACTIONS

This drug should not be used with the following medications because very serious interactions may occur: high doses of aspirin and related drugs (salicylates), cidofovir, other NSAIDs (e.g; ketorolac).

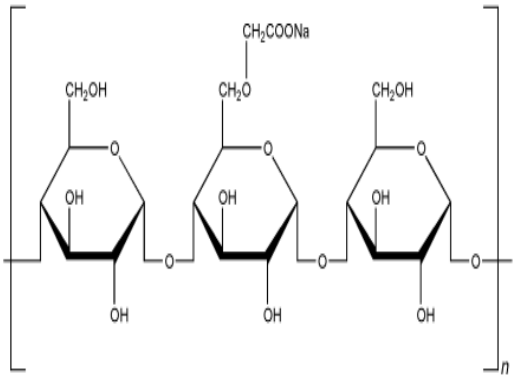
Before using this medication, especially of: anti-platelet drugs (e.g; cilostazol, clopidogrel), oral bisphosphonates (e.g; alendronate), "blood thinners" (e.g; enoxaparin, heparin, warfarin), corticosteroids (e.g; prednisone), cyclosporine, desmopressin, digoxin, high blood pressure drugs (including ACE inhibitors such as captopril, angiotensin receptor blockers such as losartan, and beta-blockers such as metoprolol), lithium, methotrexate, pemetrexed, probenecid, SSRI antidepressants (e.g; fluoxetine, sertraline), "water pills" (diuretics such as furosemide, hydrochlorothiazide, triamterene). Check all prescription and nonprescription medicine labels carefully for other pain/fever drugs (NSAIDs such as aspirin, celecoxib, ibuprofen). These drugs are similar to this medication, so taking one of these drugs while also taking this medication may increase your risk of side effects.

The possible side effects of non-steroidal anti inflammatory drugs (NSAIDS)

- Stomach pain, Gas
- Constipation, Heartburn
- Diarrhea, Nausea.

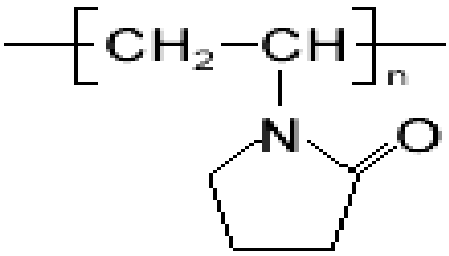
6. EXCIPIENT PROFILE

6.1 SODIUM STARCH GLYCOLATE

Nonproprietary Names	:	BP: Sodium starch glycollate PhEur: Carboxymethylamylum natricum USPNF: Sodium starch glycolate
Synonyms	:	Carboxymethyl starch, sodium salt; *Explosol*; *Explotab*; *Glycolys*; *Primojel*; starch carboxymethyl ether, sodium salt.
Chemical Name and CAS Registry Number	:	Sodium carboxymethyl starch [9063-38-1]
Structural Formula	:	
Functional Category	:	Tablet and capsule disintegrant.
Applications Pharmaceutical Formulation or Technology	:	Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%. Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time

Stability and Storage Conditions	**:**	Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.
Safety	**:**	Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

6.2 CROSPOVIDONE

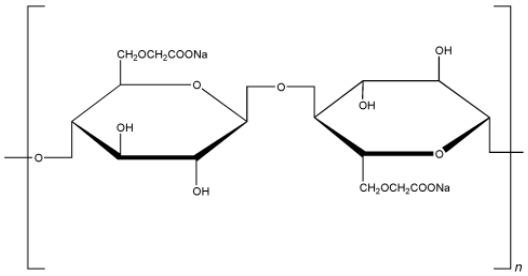
Nonproprietary Names	**:**	BP: Crospovidone PhEur: Crospovidonum USPNF: Crospovidone
Synonyms	**:**	Crosslinked povidone; E1202; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.
Chemical Name and CAS Registry Number	**:**	1-Ethenyl-2-pyrrolidinone homopolymer [9003-398]
Empirical Formula and Molecular Weight	**:**	$(C_6H_9NO)_n$ The USPNF 23 describes crospovidone as a water-insoluble synthetic crosslinked homopolymer of N-vinyl-2-pyrrolidinone.
Structural Formula	**:**	

Functional Category	**:**	Tablet disintegrant.
Applications in Pharmaceutical Formulation or Technology	**:**	Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods.
Description	**:**	Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.
Stability and Storage Conditions	**:**	Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.
Safety	**:**	Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.

6.3 CROSCARMELLOSE SODIUM

Nonproprietary Names	**:**	BP: Croscarmellose sodium PhEur: Carmellosum natricum conexum USPNF: Croscarmellose sodium
Synonyms	**:**	Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.
Chemical Name and	**:**	Cellulose, carboxymethyl ether, sodium salt,
Empirical Formula and Molecular Weight	**:**	Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium. Typical molecular weight is 90 000–700 000.

Structural Formula :



Functional Category : Tablet and capsule disintegrant

Applications : Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes.

Description : Croscarmellose sodium occurs as an odorless, white or grayish-white powder

Stability and Storage Conditions : Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

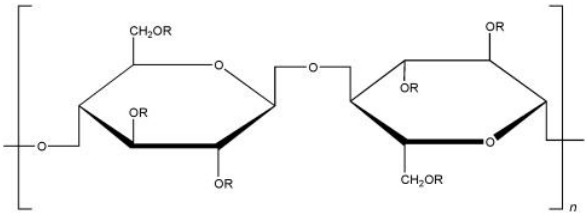
6.4 LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE

Nonproprietary Names : JP: Low-substituted hydroxypropylcellulose
USPNF: Low-substituted hydroxypropyl cellulose

Synonyms : Hyprolose, low-substituted; L-HPC.

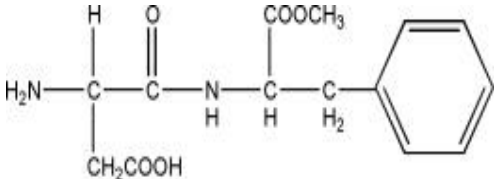
Chemical Name and Registry Number : Cellulose, 2-hydroxypropyl ether (low-substituted).

Empirical Formula : Hydroxypropoxy groups (—OCH2CHOHCH3).

Structural Formula	:	
Description	:	Low-substituted hydroxypropyl cellulose occurs as a white to yellowish white powder or granules. It is odorless or has a slight, characteristic odor, and it is tasteless.
Functional Category	:	Tablet and capsule disintegrant; tablet binder
Applications in Pharmaceutical Formulation or Technology	:	Low-substituted hydroxypropyl cellulose is widely used in oral solid-dosage forms. It is primarily used in tableting as a disintegrant, and as a binder in wet granulation.
Stability and Storage Conditions	:	Low-substituted hydroxypropyl cellulose is a stable, though hygroscopic, material. The powder should be stored in a well-closed container.
Safety	:	Low-substituted hydroxypropyl cellulose is generally regarded as a nontoxic and nonirritant material.

6.5 ASPARTAME

Nonproprietary Names	:	BP: Aspartame PhEur: Aspartamum USPNF: Aspartame
Synonyms	:	3-Amino-N-(aì-carboxyphenethyl)succinamic acid N-methyl ester;3-amino-(aìmethoxycarbonylphenethyl) succinamic acid; APM; aspartyl phenylamine methyl ester;
Chemical Name and CAS Registry Number	:	N-aò-L-Aspartyl-L-phenylalanine 1-methyl ester [22839-47-0]
Empirical Formula and Molecular Weight	:	$C_{14}H_{18}N_2O_5$ 294.31

Structural Formula : 

Functional Category : Sweetening agent

Description : Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.

Applications in Pharmaceutical Formulation or Technology : Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mix, and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste characteristics, the approximate sweetening power is 180–200 times that of sucrose. Unlike some other intense sweeteners, aspartame is metabolized in the body .

Stability and Storage Conditions : Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products.

6.6 MANNITOL

Description : Mannitol occurs as white, odorless, crystalline powder, or free flowing granules. It has sweet taste, approximately sweet as glucose.

Empirical formula : $C_6H_{14}O_6$

Molecular weight : ≅ 182.17

Functional category : Sweetening agent, tablet and capsule diluent, tonicity agent, vehicle (vehicle agent) for lyophilized preparation.

Applications in this formulation : In Pharmaceutical preparation it is primarily used as diluent (10-90%) in tablet formulations.

6.7 MAGNESIUM STEARATE

Non proprietary name	**:**	BP: magnesium stearate, JP: magnesium stearate, Ph eur:magnesii stearas, USPNF: magnesium stearate.
Synonyms	**:**	Magnesium octsdecanoate; octa decanoic acid,magnesium salt; stearic acid, magnesium salt
Chemical name and CAS registry number	**:**	Octadecanoic acid magnesium salt [557-04-0]
Functional category	**:**	Tablet and capsule lubricant
Application in pharmaceutical formulation or technology	**:**	Magnesium stearate is widely used in cosmetics, foods and in pharmaceutical formulation. It is primarily used as a lubricant in capsule and tablet manufacture.
Description	**:**	Magnesium stearate is a very fine, light white, precipitated or milld, implantable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greesy to the touch and readily adheres to the skin.
Melting range	**:**	117-150^{oc}(commercial samples); 126-130^{oc}(high purity magnesium stearate)
Solubility	**:**	Sractically insoluble in ethanol, ethanol(95%), ether and water; slightly soluble in warm benzene and warm ethanol(95%)

6.8 TALC

Nonproprietary Names	**:**	BP: Purified talc JP: Talc PhEur: Talcum· USP: Talc
Synonyms	**:**	Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc;
Chemical Name and CAS Registry Number	**:**	Talc [14807-96-6]

Empirical Formula and Molecular Weight	:	Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si2O5)_4(OH)_4$.
Description	:	Talc is a very fine, white to greyish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.
Functional Category	:	Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.
Applications in Pharmaceutical Formulation or Technology	:	Talc was once widely used in oral solid dosage formulations as a lubricant and diluent.
Stability and Storage Conditions	:	Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.
Safety	:	Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material.

7. EXPERIMENTAL INVESTIGATION

7.1. Preparation of standard graph of Naproxen sodium in distilled water

Accurately weighed amount (100 mg) of the drug was dissolved in distilled water in 100 ml volumetric flask and the volume was made up to 100ml. from this stock solution 10ml is withdrawn in to volumetric flask, made the volume up to 100ml with distilled water. From this 2nd stock solution (100mcg/ml), concentrations of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 μg/ml solutions were prepared and the corresponding absorbance was measured at 332 nm in a UV/Visible spectrophotometer (Figure 1).

7.2. Preparation of standard graph of Naproxen sodium in pH 6.8 phosphate buffer

Accurately weighed amount (100 mg) of the drug was dissolved in pH 6.8 phosphate buffer in 100 ml volumetric flask and the volume was made up to 100ml. from this stock solution 10ml is withdrawn in to volumetric flask, made the volume up to 100ml with pH 6.8 buffer. From this 2nd stock solution (100mcg/ml), concentrations of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 μg/ml solutions, were prepared and the corresponding absorbance was measured at 332 nm in a UV/Visible spectrophotometer (Figure 2).

7.3. Preparation of the tablet formulations by direct compression method

Each tablet (weight 400mg) consisted of Naproxen sodium, superdisintegrants such as crospovidone, croscarmellose sodium, sodium starch glycolate (SSG), low subsituated hydroxyl propyl cellulose (L-HPC), mannitol, aspartame, talc and magnesium stearate , prepared by direct compression method . The drug, diluent, superdisintegrant, sweetners, are passed through the sieve no. 40. All the ingredients are mixed well in the motor. Then mixed with lubricant (2 mg) for 3 min in a motor. The mixer was compressed by using 10mm flat punches on sixteen station rotary tablet compression machiene.

Table No: 4 General composition of formulation prepared by direct compression method

Formulation	F1	F2	F3	F4	F5	F6
Drug	275mg	275mg	275mg	275mg	275mg	275mg
SSG	16mg	24mg	32mg	-	-	-
CCS	-	-	-	16mg	24mg	32mg
Mannitol	103 mg	95 mg	87 mg	103 mg	95 mg	87 mg
Aspartme	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Magnesium stearate	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Talc	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Total	400mg	400mg	400mg	400mg	400mg	400mg

SSG = Sodium Starch Glycolate; **CCS =** Cros Carmellose Sodium**.**

Table No: 5 General composition of formulation prepared by direct compression method

Formulation	F7	F8	F9	F10	F11	F12
Drug	275mg	275mg	275mg	275mg	275mg	275mg
CP	16mg	24mg	32mg	-	-	-
L-HPC	-	-	-	16mg	24mg	32mg
Mannitol	103 mg	95 mg	87 mg	103 mg	95 mg	87 mg
Aspartme	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Magnesium stearate	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Talc	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Total	400mg	400mg	400mg	400mg	400mg	400mg

CP = Crospovidone; **L-HPC** = Low- substituted hydroxypropyl cellulose

7.4. Characterization of Fast Disintegrating Tablet

A. Evaluation of blends

The quality of tablet is generally dictated by the quality of physicochemical properties of blends. There are many formulation and process variables involved in mixing step and all these can affect the characteristics of blends produced.

The various characteristics of blends tested are as given below:

1. Angle of Repose

The frictional force in a loose powder can be measured by the angle of repose θ. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula

$$\tan \theta = h/r$$

Therefore $\theta = \tan^{-1} h/r$

Where θ = Angle of repose

h = height of the cone

r = Radius of the cone base

Angle of Repose less than 30^0 shows the free flowing of the material.

2. Bulk Density

Density is defined as weight per unit volume. Bulk density, ρ_b, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/ cm^3.

The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together.

Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. A standard procedure used for obtaining bulk density or its reciprocal bulkiness is given below.

A sample of about 50 cm^3 (blend) is carefully introduced in a 100ml graduated cylinder. The cylinder is dropped onto a hard wood surface three times from a height of 1 inch at two

second interval. The bulk density is then obtained by dividing the weight of sample in gms by final volume in cm^3.

$$\rho_b = M / V_p$$

Where ρ_b = Bulk Density

M = Weight of sample

V_p = Final volume of blend in cm^3

3. Tapped density

It is defined as the ratio of weight of blend in gms to the volume (Tapped volume) in cm^3. Tapped density is given by

$$\text{Tapped density } \rho_t = \text{Weight in gms} / V_b$$

Where V_t = Tapped volume (Tapped volume)

4. Compressibility Index Hausner's Ratio

It is an important measure obtained from bulk density and is defined as,

$C = \rho_b - \rho_t / \rho_b \times 100$

If the bed of particles is more compressible the blend will be less flow able and vice versa. Materials having "C" values less then 20 -21% is termed as free flowing materials.

B. Evaluation of fast disintegrating tablet

Tablets from all the formulation were subjected to following quality control test.

1) General appearance

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are tablet's size, shape, colour, presence or absence of an odor, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

2) Thickness of Tablet

Randomly 10 tablets were taken from each formulation trial batch and their thickness was measured using a Vernier caliperse. The individual tablet was placed between two anvils

and sliding knob was rotated until the tablet was tightly fitted. The digital reading displayed was noted.

3) Weight variation test

20 tablets were randomly selected from each formulation trial batch and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight.

Table No:6 Uniformity of weight

Average weight of Tablets (mg)	Maximum percentage different allowed
80 or less	±10.1
80 – 250	±7.5
More than 250	±5.0

4) Hardness

Tablet hardness, which is defined as the force required to break a tablet by radial compression, was measured with a tablet hardness tester (Pfizer/Monsato Hardness tester

5) Friability

It is measured of mechanical strength of tablets. Roche fribalator is used to determine the friability by following procedure.

Twenty tablets were weighed and placed in Roche Friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions, tablets are removed, dedusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Friability =(loss in weight / Initial weight)X 100

6) Disintegration Time

The test is carried out on the 3 tablets using the apparatus specified in USP distilled water at 37 ^{0} C ± 2 ^{0} C was used as a disintegration media and the time in second taken for complete disinigration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

7) Determination of in vivo disintegration time

A tablet was put into the mouth of a healthy male adult volunteer without water and the oral disintegration time was recorded as the time until the volunteer felt that the tablet had disappeared in his mouth while moving his tongue (n = 3).

8) Wetting time

A sample of the final tablet was placed in a Petri dish (10 cm in diameter) containing 10 ml water at room temperature. The wetting time is that necessary for the complete wetting of the tablet. Results of this test, carried out in triplicate, are shown in for the different samples.

9) In vitro dissolution

Freshly prepared phosphate buffer (pH 6.8) of 900 ml was placed in each dissolution vessels of dissolution test apparatus (USP, II paddle method). The tablets were placed in the dissolution medium. The temperature of the dissolution medium was maintained at 37± 0.5^0C and the paddle was rotated at 50 rpm. Five ml samples were withdrawn. The sample volume was immediately replaced with the same volume of fresh media as when a sample was taken. The samples withdrawn were filtered, diluted and estimated spectrophotometrically at 332 nm. Cumulative amount of the drug released at each interval was calculated by using standard graph of Naproxen sodium.

10) Water absorption ratio

A small culture Petri dish can be taken containing 6ml of water and a piece of tissue paper folded twice is placed. A tablet is placed gently on it and the time for complete wetting is measured. The wetted tablet is reweighed. Water absorption ratio R was determined according the following equation

$$R = (Wa - Wb) / Wb \times 100$$

Where Wa is the weight of tablet after water absorption and Wb is the weight of tablet before absorption.

11) Content uniformity

From each batch of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 50 ml pH 6.8 buffer of was added and then the solution was subjected to sonication for about 2 hrs. The solution was made up to the mark with pH 6.8 buffer. The solution was filtered and suitable dilutions were prepared with pH 6.8 buffer. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 332 nm by using UV-Visible spectrophotometer.

12) Fourier Transform Infrared Spectroscopy

In this study, FTIR spectra for the drug and the excipients of the optimized tablets were obtained. One part of Potassium Bromide was mixed with 100 parts of the optimized tablet powder and used for the FTIR spectrum. Pure drug was also mixed with Potassium Bromide and spectrum was obtained. Both spectra were compared for possible deviations**.**

8. RESULTS AND DISCUSSION

8.1 Preparation of standard graph of Naproxen sodium

Naproxen sodium has the maximum absorbance at 332 nm. Standard graph of naproxen sodium in water was plotted by taking concentration ranging from 10 to 100 µg/ml and a good correlation was obtained with R^2 value of 0.9991(Figure No 1). Standard graph of Naproxen sodium in pH 6.8 buffer was plotted by taking concentration ranging from 10 to 100 µg/ml and a good correlation was obtained with R^2 value of 0.999 (Figure No 2).

Table No: 7 Preparation of standard graph of Naproxen sodium in distilled water

Concentration(mcg/ml)	Absorbance(nm)
0	0
10	0.022
20	0.07
30	0.118
40	0.17
50	0.23
60	0.286
70	0.33
80	0.392
90	0.442
100	0.505

Figure No: 1 Standard graph of Naproxen sodium in water.

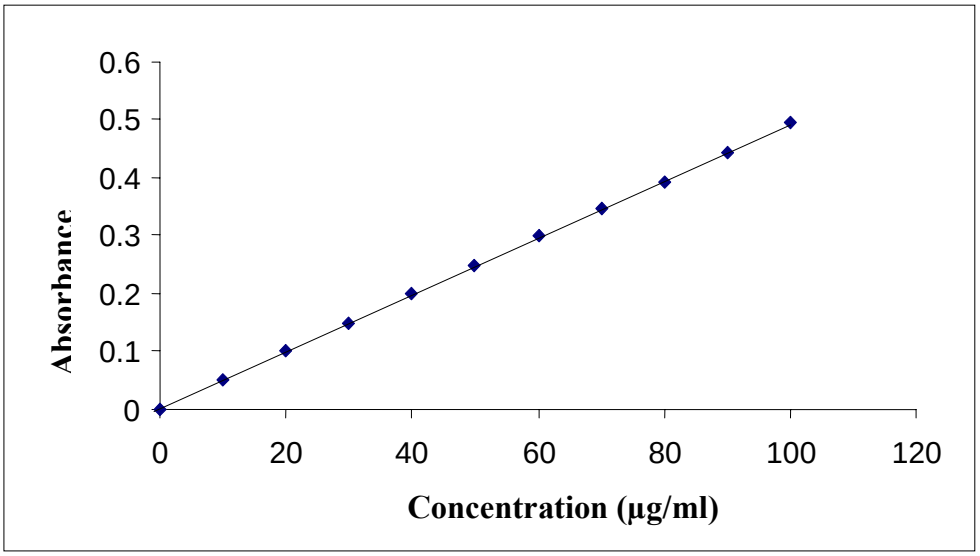
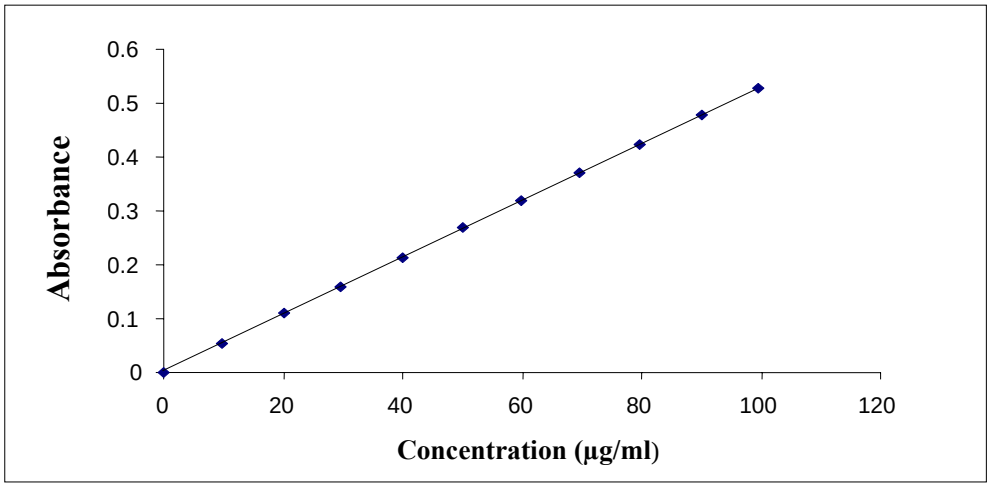


Table No: 8 Preparation of standard graph of Naproxen sodium in pH 6.8 phosphate buffer

Concentration(µg/ml)	Absorbance(nm)
0	0.000
10	0.037
20	0.099
30	0.150
40	0.206
50	0.264
60	0.312
70	0.365
80	0.409
90	0.462
100	0.524

Figure No: 2 Standard graph of Naproxen sodium in pH 6.8 buffer.



8.2 Evaluation of blend

Blend was evaluated for bulk density, tapped density, compressibility index, hausner ratio, angle of repose (Table. No 9 and 10). All the formulation show angle of repose below 30^0 that mean they show free flowing property. All the formulation has hausner ratio between the 0.7 to 1.5. It indicates all the formulation show better flow property.

Table No: 9 Evaluation of mixed blend of drug and excipients

Formulation	Angle of repose(θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility (%) index (CI)	Hausner's ratio
F1	27.61	0.38	0.52	44.51	0.90
F2	29.42	0.43	0.71	40.22	1.19
F3	26.30	0.36	0.62	36.41	1.21
F4	30.02	0.36	0.59	35.44	0.73
F5	26.81	0.40	0.62	42.35	1.15
F6	29.34	0.39	0.71	38.12	0.92
F7	29.71	0.42	0.58	37.21	0.82
F8	27.56	0.36	0.59	40.65	0.91
F9	28.41	0.42	0.61	38.71	1.25
F10	29.22	0.39	0.57	41.34	0.94
F11	30.01	0.44	0.71	34.92	1.54
F12	28.78	0.42	0.62	40.33	0.91

Table No: 10 Evaluation of Naproxen sodium tablets

Formulation	Thickness	Hardness (kg/cm^2)	Weight variation	Friability (%)	Disintegration Time in Sec.	Water Absorption ratio (%)
F1	4.17±0.05	3.5	400±1.05	0.75	47	98.24
F2	4.13±0.07	4.1	400±2.5.	0.68	43	111.91
F3	4.16±0.05	3.2	400±1.5	0.64	49	103.42
F4	4.15±0.06	4.0	400±2.9	0.61	60	101.92
F5	4.14±0.09	3.1	400±1.9	0.73	55	99.51
F6	4.15±0.07	3.5	400±1.6	0.75	50	100.24
F7	4.17±0.05	3.1	400±1.5	0.79	40	105.23
F8	4.19±0.07	4.2	400±2.6	0.68	30	106.92
F9	4.16±0.05	3.5	400±3.1	0.85	35	115.54
F10	4.15±0.06	3.9	400±2.7	0.79	94	79.31
F11	4.14±0.09	3.7	400±1.3	0.84	82	78.44
F12	4.15±0.07	3.2	400±1.6	0.87	87	73.96

8.3 Evaluation of tablets

The total weight of each formulation was not maintained constant however; the weight variation of the tablets was within the permissible limits of 5%, as specified for tablet weighing more than 400 mg(Table No 11 and 12).

The hardness of tablets was tested using hardness tester to find out whether they could retain their physical shape. The hardness of the prepared tablets were within the limits.

Tablet thickness was also used to assess the quality of tablets. Under uniform conditions of manufacture, the total weight of tablet and thickness were linearly related. The friability loss of less than 0.5 – 1% in weight is generally considered acceptable. Disintegration test was conducted for all the formulation. From the results the tablets which have crospovidone they show less disintegration time when compared with other disintegrants, in addition to its unique particle size and morphology, disintegrant properties of CP are not affected by pH and consequently being non-ionc does not bind to ionic drug moieties. The probable reason for delayed disintegration of the tablets with cros carmellose sodium, sodium starch glycolate, might be due to their tendency to gel more than crospovidone . So, it may be assumed that 8% concentration is optimum for crospovidone. 8%concentration is optimum for cross carmellose. and 4% concentration is optimum for sodium starch glycolate, disintegration occurs as a result of up take of water followed by rapid and enormous swelling. 4% concentration is optimum for L-subsituated hydroxyl propyl cellulose. Such a behaviour of super disintegrants at higher concentration may be due to blockade of capillary pores, which prevents the entry of fluid in to the tablet (Table No 11. and 12).

Water absorption study conducted for all batches crospovidone shoe more water absorption ratio. Sodium starch glycolate in second position, Cros carmellose in third position.

8.4 Content uniformity

All the formulations were checked for content uniformity as per Indian Pharmacopoeia. All the formulations passed the test and the percent of active ingredient ranged from 94.9-102.1% (Table No 13).

Table No: 11 Assay of Naproxen sodium

Formulation	Assay
F1	98.5%
F2	101.1%
F3	96.4%
F4	97.2%
F5	99.1%
F6	96.4%
F7	95.7%
F8	99.7%
F9	96.8%
F10	97.1%
F11	98.7%
F12	96.4%

8.5 Comparison of Dissolution Profile for F1 to F12 batches

In vitro dissolution study of formulations F1to F12 batches showed drug release with in 10 min, in this F8 batch show good dissolution property (Figure No 3). F8 batch contain 8% of Crospovidone.

Table No: 12 Comparison of dissolution profile for F1, F2, F3 Batches (Naproxen sodium+ Sodium starch glycolate)

Time(min)	F1 Cumulative % Drug Release	F2 Cumulative % Drug Release	F3 Cumulative % Drug Release
0	0	0	0
2	34.51	30.12	31.47
4	51.21	46.65	48.72
6	69.09	66.47	60.52
8	82.92	83.47	72.15
10	96.70	91.48	91.42

Figure No: 3 Comparison of dissolution of F1, F2, F3 batches.

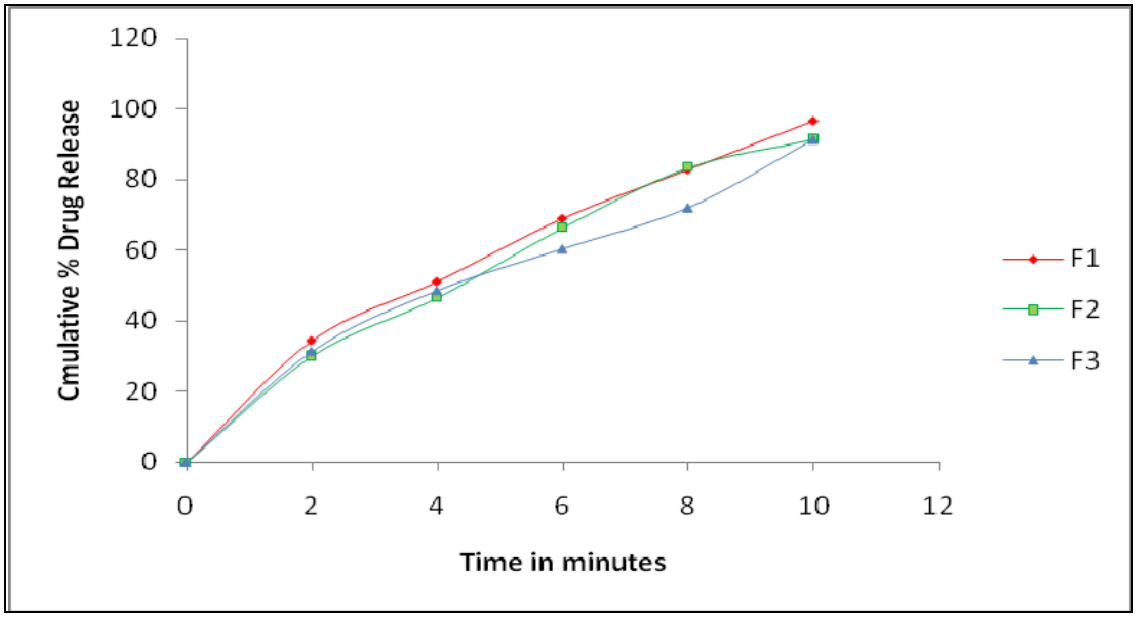


Table No: 13 Comparison of dissolution profile for F4, F5, F6 batches (Naproxen sodium+ Cros carmellose sodium)

Time(min)	F4 Cumulative % Drug Release	F5 Cumulative % Drug Release	F6 Cumulative % Drug Release
0	0	0	0
2	42.19	45.59	48.87
4	53.91	59.18	62.72
6	61.24	72.55	76.16
8	73.59	85.92	89.48
10	95.09	95.18	95.72

Figure No: 4 Comparison of dissolution of F4, F5, F6 batches.

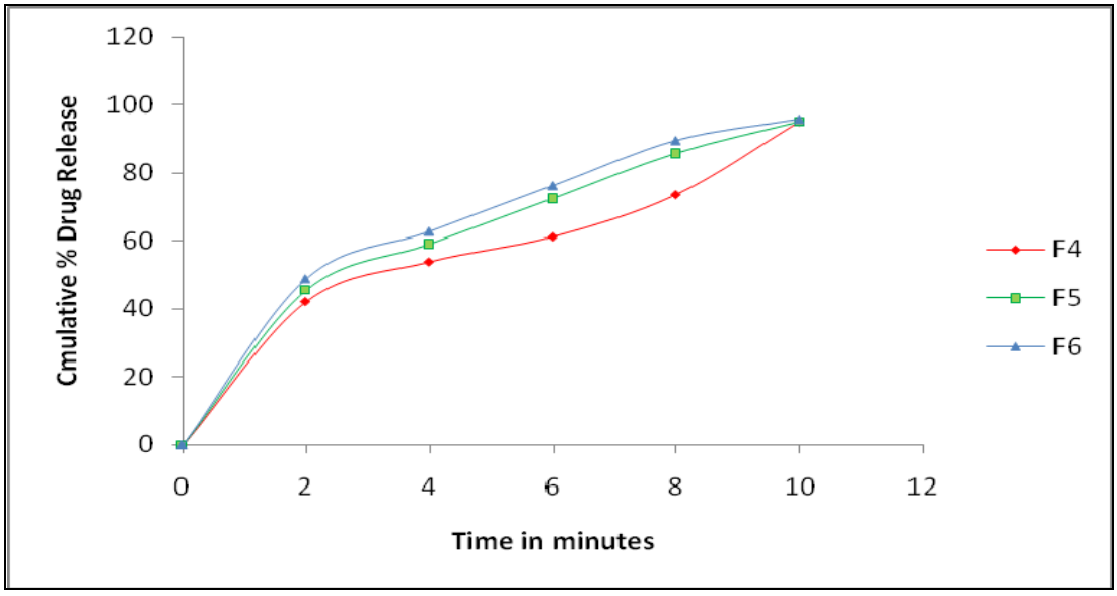


Table No: 14 Comparison of dissolution profile for F7, F8, F9 batches (Naproxen sodium+ Crospovidone)

Time(min)	F7 Cumulative % Drug Release	F8 Cumulative % Drug Release	F9 Cumulative % Drug Release
0	0	0	0
2	49.25	46.60	45.09
4	63.55	63.71	62.72
6	77.36	78.83	76.31
8	88.30	86.49	85.48
10	94.55	97.32	96.12

Figure No: 5 Comparison of dissolution of F7, F8, F9 batches.

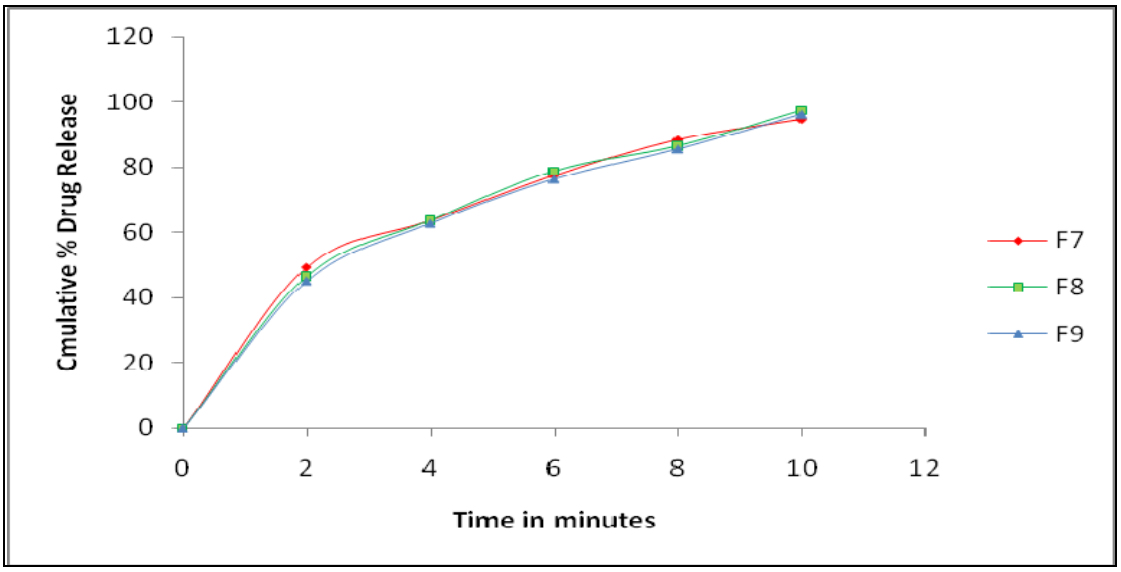
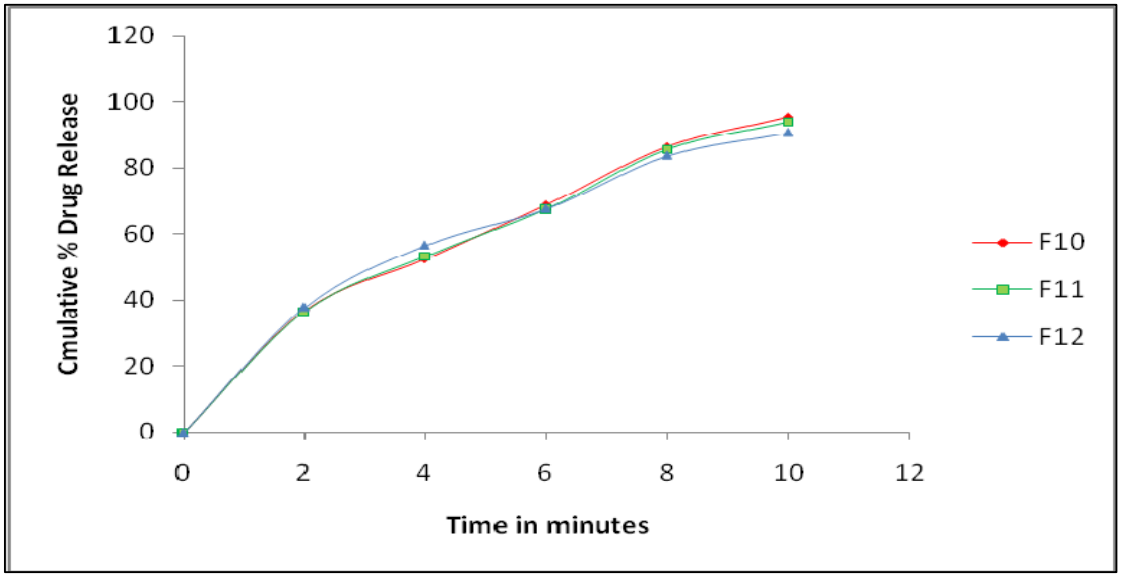


Table No: 15 Comparison of dissolution profile for F10, F11, F12 batches (Naproxen sodium+ L-HPC)

Time(min)	F10 Cumulative % Drug Release	F11 Cumulative % Drug Release	F12 Cumulative % Drug Release
0	0	0	0
2	36.85	36.56	37.89
4	52.46	53.26	56.64
6	68.85	67.51	67.69
8	86.45	85.56	83.75
10	95.45	93.86	90.71
12	98.89	97.12	94.82

Figure No: 6 Comparison of dissolution of F10, F11, F12 batches.



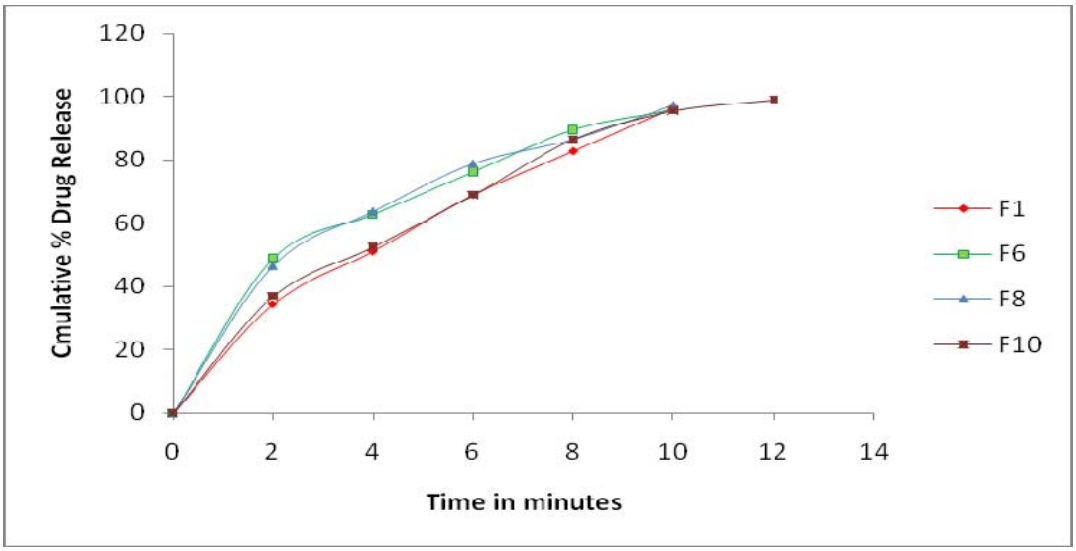
8.6 Comparison of dissolution profile for F1, F6, F8, F10 batches

In vitro dissolution study of formulation F8 batch release the drug 97.32with in 10 min and other batches showed (Figure No 7) less percentage of drug release than F8 batches (Table No 16).

Table No: 16 Comparison of dissolution profile for F1, F6, F8, F10 batches

Time(min)	F1 Cumulative % drug release	F6 Cumulative % drug release	F8 Cumulative % drug release	F10 Cumulative % drug release
0	0	0	0	0
2	34.51	48.87	46.60	36.85
4	51.21	62.72	63.71	52.46
6	69.09	76.16	78.83	68.85
8	82.92	89.48	86.49	86.45
10	96.70	95.72	97.32	95.45
12	-	-	-	98.89

Figure No: 7 Comparison of dissolution of F1, F6, F8, F 10 batches.

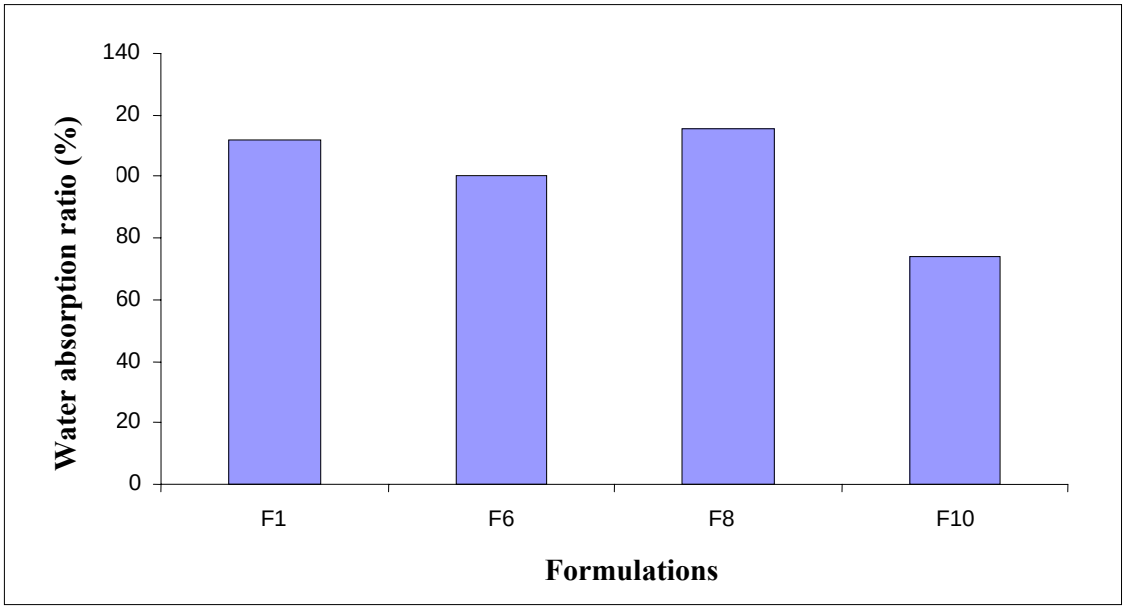


8.7 Comparison of water absorption ratio (%) of F1, F6, F8, F10 batches

Water absorption ratio (%) of F8 batch was showed the maximum water absorption ratio (%) than other batches (Figure No 8).

Formulation	Water Absorption ratio (%)
F1	98.24
F6	100.24
F8	106.91
F10	79.32

Figure No: 8 Water absorption ratios (%) of F1, F6, F8, F10 batches.



8.8 Fourier transform infrared spectroscopy

The IR spectra of pure Naproxen sodium drug showed the characteristic absorption bands are as follows: COO^- at 1585 cm^{-1}, aromatic CH_3- CH stretching at 2957 cm^{-1}, aliphatic CH_3O stretching at 2904 cm^{-1}, C-H stretching of aromatic ring at 3058 cm^{-1}, carboxyl keto group showed absorption band at 1631 cm^{-1}, naphthalene stretching at 1500 cm^{-1} and strong bending mode at 900-650 cm^{-1}.

No drug-polymer interaction was observed in the FTIR spectra of the powder mixture of optimized formulation since the absorption peaks of the drug still could be detected in the mixture.

Figure No: 9 FTIR STUDIES ON NAPROXEN SODIUM

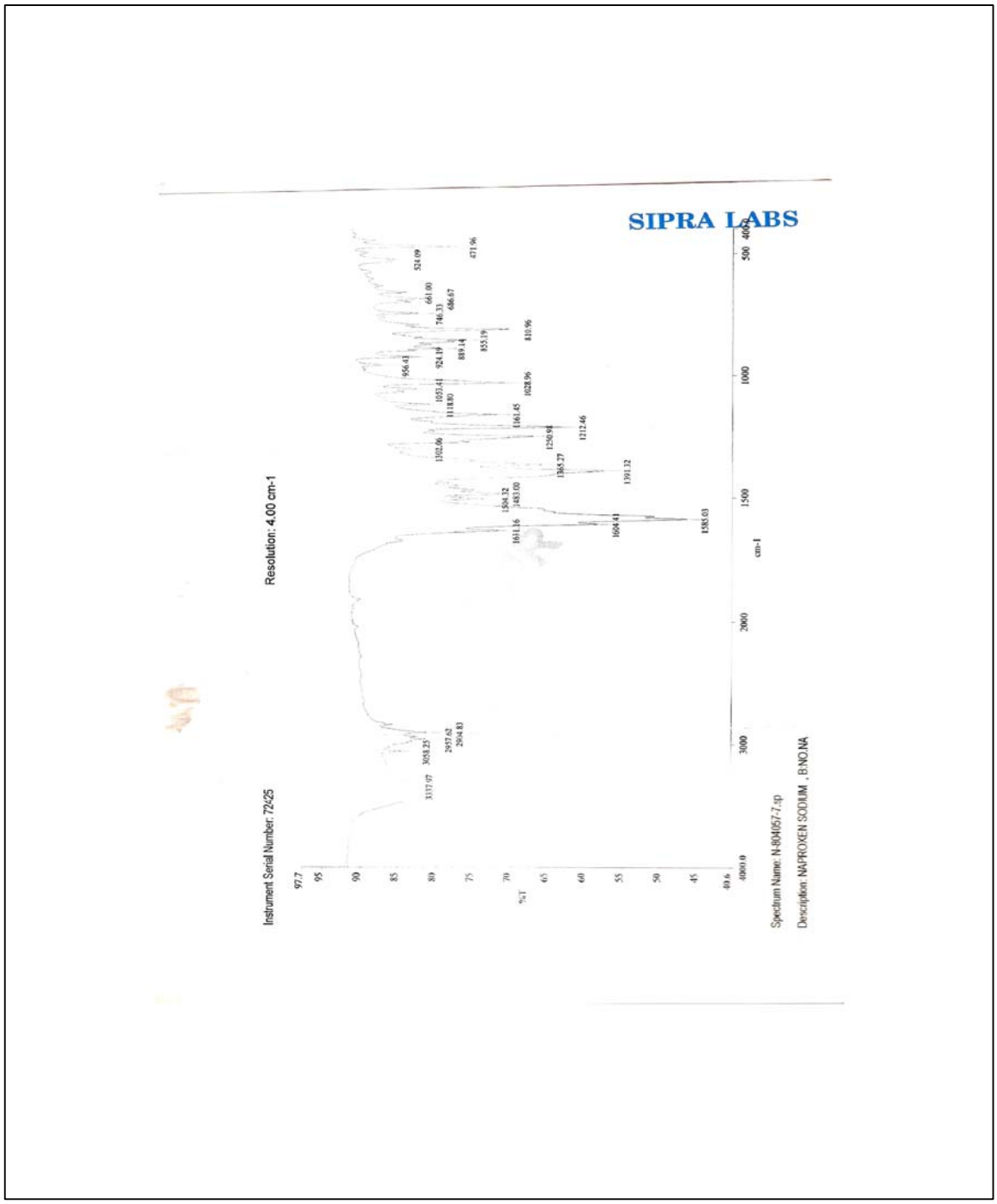


Fig. No: 10 FTIR STUDIES ON DESCRIPTION PLACED OF NAPROXEN SODIUM FDT

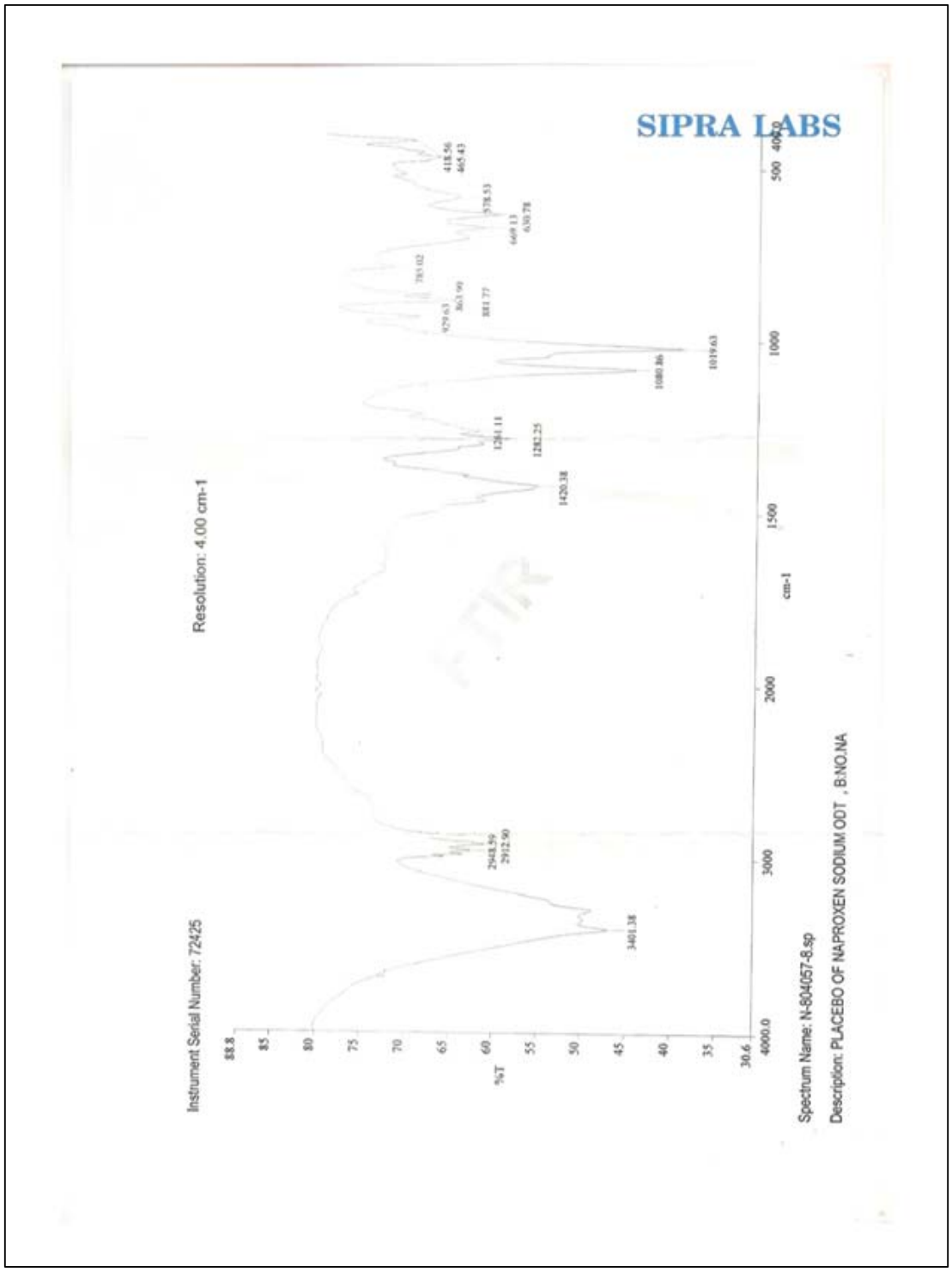
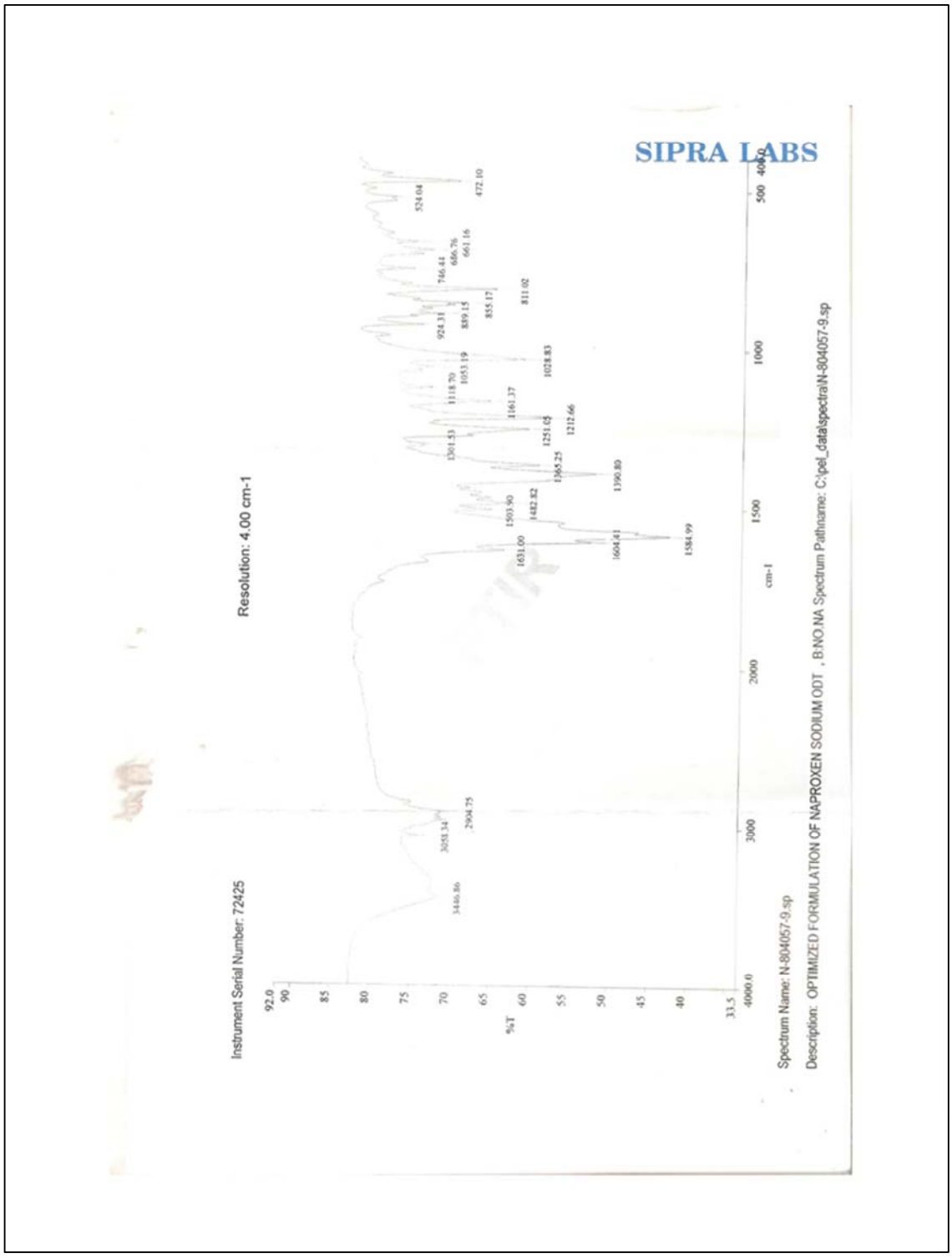


Fig. No: 11 FTIR STUDIES ON OPTIMIZED FORMULATION OF NAPROXEN SODIUM FDT



9. STABILITY STUDY OF TABLET BATCH

The batch F8 are selected as an optimum batch and the stability study was carried out at accelerated condition of 40^0C, 75 % RH condition for a period of three months.

Method:

The tablets were individually wrapped using Aluminium foil and packed in ambered color screw cap bottle and put at above specified condition in incubator for 3 months. After three months tablets were evaluated for content uniformity and *In-vitro* drug release.

Observation:

The results of stability study after 3 months are given in Table. No: 19.

The plot of Cumulative percentage Drug release v/s Time deplicated in Fig. No: 12.

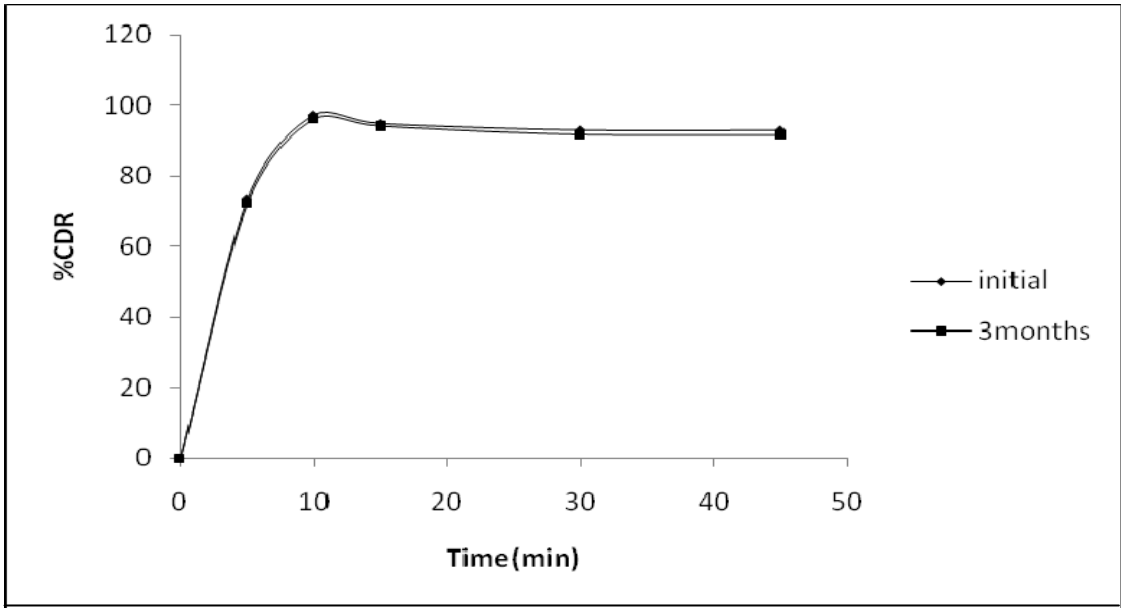
Drug content:

Comparative content uniformity of the tablet after 3 months stability.

Table No: 17 Dissolution Profile of batch F8 kept for stability of Three months

	Time in (minutes)	Cumulative % drug release	
		Initial	3 Months
		F8	F8
Dissolution medium 900ml 0.1N HCL	5	73.60	72.65
	10	97.32	96.89
	20	94.83	94.12
	30	92.95	91.98
	45	92.93	91.88

Fig No: 12 Dissolution profile of F8 Initial and Three Months



10. SUMMARY & CONCLUSION

Fast disintegrating tablets of Naproxen sodium prepared by direct compression method The *in vitro* drug release from formulation containing superdisintegrant SSG was found between 87.64 to 96.70 in 10 min and the maximum drug release was found with F1 formulation. The *in vitro* drug release from formulation containing superdisintegrant CCS was found between 94.20 to 95.72 in 10 min and the maximum drug release with F6 formulation. The *in vitro* drug release from formulation containing superdisintegrant CP was found between 90.75 to 97.32 in 10 min and the maximum drug release with F8formulation. The *in vitro* drug release from formulation containing superdisintegrant L-HPC was found between 94.82 to 98.89 in 12 min and the maximum drug release with F10 formulation.

Fast disintegrant tablets transform into easy-to-swallow suspension on contact with the saliva, after ingested in mouth. These are particularly useful for pediatric or geriatric patients, can be taken without liquids. The developed formulations have suitable characteristics. Among the four superdisintegrants, Crospovidone (F8) showed good disintegrants property. It has also shown good water absorption ratio.

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